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ORIGINAL ARTICLE

Improvement of exercise performance and ventilatory efficiency in patients with chronic heart failure after sildenafil use for 8 weeks

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KEYWORDS

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Abstract *Background:* Heart failure (HF) is frequently complicated by elevated pulmonary vascular resistance associated as a result of dysregulation of nitric oxide-mediated vascular smooth muscle tone. The resulting pulmonary hypertension directly affects right ventricular function and may affect exercise capacity, morbidity, and mortality. Sildenafil, a type 5 phosphodiesterase inhibitor, lowers pulmonary vascular resistance in pulmonary hypertension by increasing intracellular levels of the nitric oxide. The aim of the study was to evaluate the improvement of exercise performance, ventilatory efficiency, and pulmonary hypertension after 8 weeks of regular sildenafil use in outpatients with CHF.

Methods and results: Forty patients with controlled heart failure on standard antifailure treatment were enrolled in this study. Half of them received sildenafil 50 mg twice daily for 8 weeks and the other half was taken as a control group. Echo-Doppler, cardiopulmonary exercise testing, and clinical follow-up were done. There was a statistically significant drop of PAP in the sildenafil group from 58.4 ± 2 mmHg to 40.3 ± 0.5 mmHg and improvement in VO_2 Peak, VE/VCO_2 slope, $\text{T-1/2 } \text{VO}_2$ (min) and $\text{T-1/2 } \text{VCO}_2$ (min) from 17.2 ± 2 , 39.1 ± 6 , 2.0 ± 0.5 and 2.0 ± 0.4 to 20 ± 2.5 , 42.1 ± 5 , 1.9 ± 0.7 and 1.8 ± 0.2 respectively ($p < 0.05$). Seven patients of the sildenafil group (35%) showed improvement of functional class from NYHA class II to class I. Concerning cardiac events during follow up period, as regards active group, decompensated heart failure occurred in 1 patient (5%), ischemia occurred in 1 patient (5%), and arrhythmias occurred in 2 patients (10%), while in the control group, decompensated heart failure occurred in 7 patients (35%), ischemia

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occurred in 4 patients (20%), and arrhythmias occurred in 5 patients (25%), no CVA occurred in both groups.

Conclusions: The present study showed that in patients with systolic HF, type 5 phosphodiesterase inhibition with sildenafil lowers the pulmonary artery pressure significantly and improved ventilatory efficiency monitored by VE/VCO₂ slope, oxygen uptake kinetics and also improved exercise performance.

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Introduction and aim of the work

Despite multiple pharmacologic and non-pharmacologic strategies for the management of chronic heart failure (CHF), most patients report some limitation in their exercise capacity during the natural course of the syndrome [1]. In fact, exercise intolerance dominates the clinical presentation of moderate to severe CHF and is a major determinant of overall prognosis [2].

Multiple mechanisms seem to interfere with exercise performance in CHF, including central (cardiopulmonary) and peripheral (vascular) components. In particular, pulmonary hypertension is an important predictor of functional disability in CHF [3].

Endothelial dysfunction is also a well-recognized feature of CHF that has been implicated in both its clinical presentation and prognosis [4]. Endothelial dysfunction in CHF is associated with reduced vascular nitric oxide (NO) release [3].

Inhibition of 5'-phosphodiesterase by sildenafil has proven to be beneficial in different scenarios where endothelial function and vascular tone can be positively influenced [5].

These beneficial effects are mediated in part by increases of NO availability to the vascular bed [6]. Moreover, a growing body of evidence shows that sildenafil consistently improves pulmonary hypertension caused by conditions other than CHF [7].

Later, Lewis and coworkers showed that sildenafil improved functional capacity and decreased pulmonary pressure in patients with CHF [8].

The aim of the study was to evaluate the effect of a 50 mg dose twice daily of sildenafil on exercise performance, ventilatory efficiency, oxygen uptake kinetics, pulmonary hypertension after 8 weeks in outpatients with CHF.

Patients and methods

This study was conducted at Benha University Hospital and it included 40 patients with chronic heart failure receiving standard medical therapy for CHF.

These patients were divided randomly into two equal groups:

Group (I): the control group that received the standard anti-failure therapy.

Group (II): the active group that received 50 mg sildenafil twice daily in addition to standard medical therapy.

Inclusion criteria:

- (1) Patients with chronic left ventricular systolic dysfunction (left ventricular ejection fraction more than 30% and less than 50%) on standard medical therapy for CHF [9].

- (2) All included patients were more than 20 years of age and clinically stable for at least 2 months before inclusion in the study.

- (3) Good functional capacity determined on the basis of the patients ability to perform certain daily tasks (average 4–10 METS).

Exclusion criteria:

- (1) History of intolerance to sildenafil.
- (2) Concomitant use of nitrates.
- (3) Systolic arterial pressure less than 90 mmHg.

All patients included in the study were subjected to careful history analysis, full clinical examination, baseline Echo-Doppler study particularly focusing in assessment of the LV function and pulmonary artery pressure, and baseline cardiopulmonary exercise testing.

These patients were followed up over a period of 8 weeks looking particularly for the functional class, cardiac decompensation, ischemic attacks, arrhythmias and CVA. Follow up of Echo-Doppler, and cardiopulmonary exercise testing was done at the end of the 8 weeks.

Echo-Doppler assessment of PASP

Echo-Doppler study was performed using a commercially available ultrasound machine equipped with a 2.5-MHz transducer (Vivid7), using harmonic imaging. Estimation of PASP was performed by summing the pressure gradient between the right atrium and right ventricle (in the presence of tricuspid regurgitation) and the estimated right atrial pressure. Right atrial pressure was calculated according to inferior vena cava diameter and collapsibility index [10].

Left ventricular end-systolic and end-diastolic dimensions were obtained from the parasternal short axis or long axis view, and left ventricular fractional shortening and ejection fraction were calculated [11].

Cardiopulmonary exercise testing

Maximal functional capacity was obtained by an ergospirometric examination performed on a treadmill (Jaeger ER 900) through an incremental exercise test and expired gas analysis. [8] A ramp-staged protocol was used, starting at 2.4 km/h with an inclination of 1% to 2%, followed by progressive speed increments of 0.1 to 0.12 km/h every 20 s, and 0.5% to 1.0% increases in slope every 60 s, until volitional fatigue was reached.

Gas exchange and ventilatory variables were analyzed using a calibrated computer-based exercise system (Cortex Biophysik Metalyzer 3B Stationary CPX system, MI3B2.1, Leipzig, Germany).

Data were obtained breath by breath and expressed as 15-s averages. VO_2 peak was defined as the highest value of oxygen consumption in the final 15-s period of exercise.

Ventilatory efficiency was estimated using the relationship between minute ventilation (VE) and carbon dioxide output (VCO_2), by linear regression model using all data points obtained during the cardiopulmonary exercise test.

The following parameters were obtained to assess functional capacity of the patients:

- (1) VE peak (L/min); minute ventilation = tidal volume X respiratory rate.
- (2) VO_2 peak (ml/kg/min); O_2 consumption.
- (3) VCO_2 peak (L/min); maximum CO_2 production.
- (4) R peak; VO_2 peak/ VCO_2 peak.
- (5) VE/ VCO_2 slope; minute ventilation/ CO_2 production.
- (6) T-1/2 VE (min); Half time of minute ventilation.
- (7) T-1/2 VO_2 (min); Half time of O_2 consumption.
- (8) T-1/2 VCO_2 (min); Half time of CO_2 production.

Results

Among the thirty patients with HF participated in the present study, baseline patient characteristics, etiological factors of heart failure and medications were nearly matched among both groups with no significant difference between them. All patients had undergone optimization of their HF pharmacotherapy before enrollment in the study. All patients in this study had NYHA functional class I–II at the entry of the study. None of the patients had evidence of a significant underlying pulmonary disease.

Echo-Doppler data obtained at baseline and after 8 weeks showed no significant difference between both groups regarding EF of the LV all through the study period however the PASP that was comparably elevated in both groups at the start of the study showed a significant drop in the sildenafil group after 8 weeks with no change in the placebo group.

Regarding Cardiopulmonary Exercise Test Parameters, a significant improvement in VO_2 Peak, VE/ VCO_2 slope, T-1/2 VO_2 (min) and T-1/2 VCO_2 (min) occurred, from 17.2 ± 2 , 39.1 ± 6 , 2.0 ± 0.5 and 2.0 ± 0.4 to 20 ± 2.5 , 42.1 ± 5 , 1.9 ± 0.7 and 1.8 ± 0.2 respectively ($p < 0.05$), while in the control group, there was no significant improvement in all parameters.

Clinical follow up of the patients showed that decompensated heart failure occurred in 1 patient (5%) of the sildenafil group, ischemia occurred in another patient (5%) and arrhythmias occurred in 2 patients (10%), while in the control group, decompensated heart failure occurred in 7 patients (35%), ischemia occurred in 4 patients (20%), arrhythmias occurred in 5 patients (25%) which is statistically significant, no CVA occurred in both groups during follow up period. Concerning mortality during follow up period, there was no mortality cases in the both groups.

Discussion

Because sildenafil is a potent pulmonary vasodilator, even more than inhaled nitric oxide however, it is not pulmonary vascular specific. [12] We conducted our study to investigate whether a 50 mg dose twice daily of sildenafil could improve exercise performance, ventilatory efficiency, oxygen uptake kinetics, pulmonary hypertension after 8 weeks in outpatients with CHF.

The protocol of sildenafil use was variable across the different studies, in the current study, the patients received sildenafil 50 mg twice daily for 8 weeks, while Chockalingam, et al., gave sildenafil at 50 mg twice daily for 4 weeks, and increased to 100 mg bid for 4 more weeks in a step up protocol. [13] Also Sastry [14] gave sildenafil 25 to 100 mg tid on the basis of body weight for 6 weeks and Galie et al. [15] gave sildenafil 20 mg to 10 patients, 40 mg to 15 patients, 80 mg to 20 patients orally three times daily for 12 weeks.

According to our regimen some patients reported side effects from sildenafil in the form of flushing in 4 patients (20%), headache in 2 patients (10%) and diarrhea in 1 patient (5%), however these side effects did not interrupt treatment.

The ages of the patients in the current study ranged from 36 to 72 years, with mean age 54 ± 18 years, the majority of them (65%) were below 60 years of age and male (Table 1). While Humbert et al. [16] investigated 10 patients (2 males & 8 females), mean age 34.5 ± 3.3 years also Chockalingam et al. [13] investigated 15 patients (10 males & 5 females), mean age 44.5 ± 5.3 years.

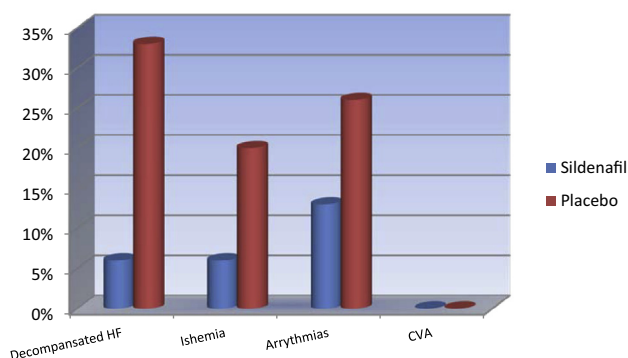
This study was evaluating the effect of sildenafil on patients with mild heart failure as all patients were in functional class (I–II) at the entry of the study after optimized and intensified treatment. However, Chockalingam et al. [13] investigated the patients who were severely symptomatic dyspnea NYHA class (III–IV) while Humbert et al. [16] investigated patients who presented with dyspnea NYHA class (II) (50%) and NYHA class III (50%).

Regarding the clinical follow up, seven patients (35%) of the sildenafil group who presented with dyspnea grade (II), showed subjective improvement to dyspnea grade (I), while in the control group, there was no significant improvement in the grade of dyspnea in the studied population, This was in concordance with Humbert et al. [16] who reported that four patients (40%) who were presented with dyspnea NYHA class III showed improvement in the grade of dyspnea (3 improved to class II and one improved to class I) on regular sildenafil intake of 50 mg t.d.s. for 3 months.

On the other hand, concerning adverse cardiac events during follow up period, there was statistically significant difference between the two groups. Decompensated heart failure occurred in 1 patient (5%) of the sildenafil group vs 7 patients (35%) of the control group (P value < 0.05), new onset ischemia occurred in 1 patient (5%) of the sildenafil group vs 4 patients (20%) of the control group (P value < 0.05) and documented arrhythmias occurred in 2 patients (10%) of the active group vs 4 patients (26%) of the control group (P value < 0.05), no CVS occurred in both groups (Fig. 1). While Humbert et al. [16] reported decompensated heart failure in 2 patients (20%), arrhythmia in 3 patients (30%), with regular sildenafil intake 50 mg t.d.s. for 3 months. However, Galie

Table 1 Baseline patient characteristics.

		Sildenafil		Control		P value
		No	%	No	%	
Age	> 60	7	35	8	40	(0.05)
	< 60	13	65	12	60	
Sex	Male	13	65	13	65	(0.05)
	Female	7	35	7	35	
HTN	Yes	7	35	10	50	(0.05)
DM	Yes	12	60	10	50	(0.05)
Smoking	Yes	12	60	10	50	(0.05)
Dyslipidemia	Yes	12	60	15	75	(0.05)
Family history	Yes	10	50	13	65	(0.05)
Obesity		9	45	13	65	(0.05)
<i>etiology of heart failure</i>						
Ischemic		5	25	7	35	> 0.05
Valvular		3	15	4	20	> 0.05
Others		12	60	9	45	> 0.05
<i>Medications</i>						
Diuretics		20	100	20	100	> 0.05
Beta-blockers		19	95	17	85	> 0.05
ACE-inhibitor		20	100	20	100	> 0.05
Digoxin 20		20	100	13	65	> 0.05

**Figure 1** Cardiac events in the studied group.

et al. [15] reported that no statistically significant clinical worsening was observed with sildenafil as compared with placebo.

Regarding mortality during follow up period, there were no mortality cases in the two groups. Kothari and Duggal [17] reported that 2 of 14 patients died after 6 and 7 months of daily dose of 150 mg sildenafil.

In the current study, cardiac events at follow up were reported more in patients aged ore than 60 years (31.1% vs. 20%, $p < 0.05$). This is consistent with Chockalingam et al. [13] that reported significant complication at 2 month follow up among patients aged more than 60 years. On the other hand Sastry [14] found no significant complication difference in

between patients aged less than 60 years and older at 6 week follow up.

Regarding Echo-Doppler follow up, in the current study, the mean PASP before giving the sildenafil was 58.4 ± 2 mmHg which was significantly reduced to 40.3 ± 0.5 mmHg after 8 weeks of regular sildenafil intake, so there was a reduction in mean PASP 18 ± 1.5 mmHg (average 30%) (P value < 0.05), while in the control group, there was no significant reduction in mean PASP (P value > 0.05) (Table 2). These results were concordant with results of Guazzi et al. [18] who reported a reduction in mean PASP values (up to 20%), however, there was no change in cardiac output. This was supported by the results of Chockalingam et al. [13] who reported a decrease in mean pulmonary artery pressure (up to 25%) with sildenafil 50 mg bid at 4 weeks also Jackson et al. [19] who reported that sildenafil 100 mg PO reduced basal PASP by 27% in men with ischemic heart disease. Galiè et al. [15] reported that all sildenafil doses (20, 40, 80 mg) orally three times daily for 12 weeks reduced the mean pulmonary artery pressure $P = 0.04$, $P = 0.01$ and $P < 0.001$, to $P = 0.003$, $P < 0.001$ and $P < 0.001$, respectively.

As regards the study of cardiopulmonary function test, patients were assessed 8 weeks after sildenafil intake and significant improvement in VO_2 Peak, VE/VCO_2 slope, $T-1/2$ VO_2 and $T-1/2$ VCO_2 (min) from 17.2 ± 2 , 39.1 ± 6 , 2.0 ± 0.5 and 2.0 ± 0.4 to 20 ± 2.5 , 42.1 ± 5 , 1.9 ± 0.7 and 1.8 ± 0.2 respectively occurred (P value < 0.05) (Table 3). This was in concordance with Wong et al. [20] who reported significant

Table 2 Echo-Doppler data.

	Sildenafil		P value	Control		P value
	Before	After		Before	After	
EF	40 ± 1.0	38 ± 2.0	> 0.05	39 ± 1.0	38 ± 0.5	> 0.05
PASP	58 ± 2	40 ± 0.5	> 0.05	57 ± 1	55 ± 1	> 0.05

Table 3 Cardiopulmonary exercise test parameters.

	Control		Sildenafil	
	Before	After	Before	After
<i>Peak exercise</i>				
VE peak, L/min ⁻¹	49 ± 11	50 ± 10	50 ± 11	55 ± 12
VO ₂ peak, mL/kg ⁻¹ /min ⁻¹	16.4 ± 3	17 ± 2	17.2 ± 2	20 ± 2.5
VCO ₂ peak, L/min ⁻¹	20 ± 7	20 ± 6	18 ± 3	19 ± 3
R peak	1.04 ± 0.1	1.05 ± 0.1	1.03 ± 0.1	1 ± 0.1
<i>Ventilatory efficiency</i>				
VE/VCO ₂ slope	44.7 ± 6	44.9 ± 6	39.1 ± 6	42.1 ± 5
<i>Recovery gas exchange</i>				
T-1/2 VO ₂ (min)	2.6 ± 0.7	2.66 ± 0.8	2.66 ± 0.8	1.9 ± 0.7
T-1/2 VCO ₂ (min)	2.5 ± 1	2.6 ± 0.9	2.6 ± 0.9	1.8 ± 0.2

improvement in peak VO₂, Peak O₂ pulse, VE/VCO₂ and P_{ET} CO₂ from 0.84 ± 0.1 L/min, 6.1 ± 0.7 ml. beat⁻¹, 49 ± 2 and 26 ± 1.5 mmHg to 0.91 ± 0.1 L/min, 6.8 ± 0.8 ml. beat⁻¹, 43 ± 2 and 30 ± 1.9, respectively after adding sildenafil 50 mg twice daily for 4 months.

Conclusion

According to our study, sildenafil is beneficial in alleviating the morbidity of mild heart failure subjectively as assessed by functional class and objectively as assessed by cardiopulmonary exercise testing.

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